Parenteral nutrition selectively decreases protein synthesis in the small intestine

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Dudley, Mary A., Linda J. Wykes, Alden W. Dudley, J R., Douglas G. Burrin, Buford L. Nichols, Judy Rosenberger, Farook Jahoor, William C. Heird, and Peter J. Reeds. Parenteral nutrition selectively decreases protein synthesis in the small intestine. Am. J. Physiol. 274 (Gastrointest. Liver Physiol. 37): G131–G137, 1998.—We investigated the effects of an elemental diet fed parenterally or enterally on total mucosal protein and lactase phlorizin hydrolase (LPH) synthesis. Catheters were placed in the stomach, jugular vein, and carotid artery of 12 3-day-old pigs. Half of the animals were given an elemental regimen enterally and the other half parenterally. Six days later, animals were infused intravenously with [3H]leucine for 6 h and killed, and the midjejunum of each animal was collected for analysis. The weight of the midjejunum was 8 ± 1.5 and 17 ± 1.6 g in parenterally fed and enterally fed pigs, respectively. LPH activities (µmol·min⁻¹·g protein⁻¹) were significantly higher in parenterally vs. enterally fed pigs. Total small intestinal LPH activities were lower in parenterally vs. enterally fed animals. The abundance of LPH mRNA relative to elongation factor-1α mRNA was not different between groups. The fractional synthesis rate of total mucosal protein and LPH was significantly lower in parenterally fed animals (67 ± 7 and 66 ± 7%/day, respectively) than in enterally fed animals (96 ± 7 and 90 ± 6%/day, respectively). The absolute synthesis rate (the amount of protein synthesized per gram of mucosa) of total mucosal protein was significantly lower in parenterally fed than in enterally fed pigs. However, the absolute synthesis rate of LPH was unaffected by the route of nutrient administration. These results suggest that the small intestine partially compensates for the effects of parenteral feeding by maintaining the absolute synthesis rate of LPH at the same levels as in enterally fed animals.

brush border; enteral; lactase phlorizin hydrolase

TOTAL PARENTERAL NUTRITION, introduced to clinical medicine about 30 years ago, is usually considered a major advance in the nutritional support of a wide range of patients who cannot tolerate enteral feeding. However, this form of nutritional support may have a profoundly negative effect on small intestinal mass and function, leading to an apparent decrease in digestive capacity (7, 17, 20, 24). The reduced digestive capacity appears to result in part from the reduced abundance of the brush-border (BB) hydrodases, which are responsible for the terminal stages of digestion (17, 24). In parenterally nourished rats, for example, total lactase phlorizin hydrolase (LPH) enzyme activity is 44% lower than that of enterally fed animals (20). Likewise, in humans, LPH enzyme activity is decreased fourfold by parenteral feeding (17).

LPH is an essential small intestinal digestive enzyme of newborn mammals and is responsible for the hydrolysis of lactose (the predominant sugar of mammalian milk) to glucose and galactose, which are in turn absorbed (13). Thus the synthesis and abundance of LPH are vitally important to the well-being of newborn animals, and a decrease in enzyme activity is of major physiological importance.

BB LPH is a glycoprotein synthesized only in the villus enterocyte. Enzyme synthesis is a complex process controlled by a series of transcriptional and posttranscriptional events that culminate in insertion of the mature protein into the BB membrane (8–10, 12, 13). Gene transcription starts in the cells at the base of the villus (12). The first detectable precursor form of the enzyme is translated and cotranslationally glycosylated in the endoplasmic reticulum to form a highmannose LPH precursor (proLPH₁; Ref. 8). In the Golgi apparatus, proLPH₁ is converted to the complex glycosylated precursor (proLPH₂), which in turn is translocated to the BB membrane (8). Either during translocation or immediately after insertion of the enzyme into the BB membrane, proLPH₂ is proteolytically cleaved to form the mature BB protein (8). Thus, as a result of its complex biosynthesis, LPH expression in the BB membrane can potentially be controlled by factors that regulate mRNA abundance and/or the rate of multiple steps of posttranscriptional synthesis.

Previous comparisons of parenteral vs. enteral feeding on intestinal morphology and function have generally compared parenteral administration of an elemental diet with enteral administration of a complex diet, making it impossible to distinguish between the effects of the route of dietary administration vs. the nature of the diet (15, 16). Furthermore, these studies have not examined the kinetics of synthesis of an essential digestive protein such as BB LPH. The present study was designed to examine in neonatal pigs the effect of parenteral vs. enteral administration of an elemental diet on mucosal protein synthesis in general, BB LPH activity, and the steps of BB LPH synthesis. We hypothesized that the rate of small intestinal protein synthesis is determined in part by the route of nutrient administration and that a decrease in BB LPH synthe-
sis might result from a decrease in the posttranslational processing rate of precursor LPH polypeptides.

**MATERIALS AND METHODS**

### Materials

All amino acids for the elemental diets were obtained from Ajinomoto (Raleigh, NC). Intralipid (20%) and dextrose were obtained from Baxter-Travenol (Deerfield, IL), and Polycolyte was obtained from Ross Laboratories (Columbus, OH). Solutions of calcium gluconate, potassium phosphates, potassium acetate, NaCl, MgSO₄, ZnSO₄, and MnSO₄ used in preparing the elemental diets were obtained from Fujisawa (Deerfield, IL). The MVI pediatric vitamin and multitrace pediatric mineral solutions were obtained from Rorer Group (Fort Washington, PA). L-[3,3,3-2H₃]leucine ([2H₃]leucine) was purchased from Cambridge Isotope Laboratory (Andover, MA). Dulbecco's phosphate-buffered saline was obtained from Gibco (Grand Island, NY), and leupeptin, aprotinin, and antipain were obtained from Sigma (St. Louis, MO). Ultra-pure hydrochloric acid (12 M) was purchased from J. T. Baker Chemical (Phillipsburg, NJ). All other chemicals were of the highest analytical grade available. All aqueous solutions were prepared with deionized water (Millipore, Bedford, MA).

### Experimental Design

The protocol for these studies was approved by the Animal Care and Use Committee of Baylor College of Medicine and was carried out in accordance with the Guide for the Care and Use of Laboratory Animals [DHHS publication no. (NIH) 85–23, revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205].

Twelve 3-day-old piglets (2 animals from each of 6 litters) were obtained from the commercial swine herd at Texas A&M University, College Station, TX, and were housed individually in rooms with an ambient temperature of 25°C. The animals were anesthetized with 5% isoflurane (Aerrane, Anaquest, Liberty Corner, NJ), and catheters were inserted into the jugular vein and the carotid artery as previously described (31–33). A percutaneous catheter was also inserted into the stomach and sutured to the stomach wall. The catheters were tunneled subcutaneously and exteriorized between the scapulae.

Piglets were fitted with a jacket to house the catheters and to facilitate administration of the elemental diets through a tether/swivel apparatus (31–33). Piglets were allowed to recover from surgery for 3 h and were divided by weight into two dietary treatment groups. That is to say, the heaviest piglet was assigned to the first treatment group, the next two heaviest (animals 2 and 3) were assigned to the second treatment group, the next two heaviest (animals 4 and 5) were assigned to the first treatment group, the next two (animals 6 and 7) to the second treatment group, and so on. The final (lightest) animal was assigned to the first treatment group. One treatment group was fed the elemental diet via the jejunal catheter (parenterally fed); the other was fed the elemental diet intragastrically (enterally fed).

As previously described, the elemental diets were designed to provide all the nutrients required by neonatal piglets for normal growth and tissue accretion (Table 1) (31–33). The parenteral and enteral infusates were identical, except that a short-chain glucose polymer (Polycolyte) was substituted for glucose as the carbohydrate source of the enteral infusate to reduce osmolality. The desired total energy intake of 220 kcal·kg⁻¹·day⁻¹ was achieved within 48 h of surgery. Twenty-six percent of energy was supplied by amino acids, 43% as glucose, and 31% as lipid. Macronutrient intakes were as follows (in g·kg⁻¹·day⁻¹): amino acids 13.5, glucose 25.4, and lipid 6.8. After 6 days on their respective regimens, conscious, unrestrained piglets were given a continuous infusion of 45 μmol·kg⁻¹·h⁻¹ of [2H₃]leucine in 0.45 g liter⁻¹ saline via the jugular vein catheter for 6 h. A 5-ml sample of arterial blood was taken before the infusion and at 30, 60, 120, 180, 240, 300, and 360 min. Blood was drawn into prechilled tubes containing Na₂-EDTA and centrifuged immediately at 4°C at 1,200 g for 15 min. Plasma was removed and stored at −70°C for later analysis.

At the end of the infusion, the pigs were killed by intravenous injection of 0.33 ml/kg of Beuthanasia-D (Schering-Plough Animal Health, Kenilworth, NJ). The entire small intestine from the peritoneal reflection (analogous to the ligament of Treitz) to the ileocecal junction was excised immediately and placed in iced saline. The small intestine was cut in half, and the proximal half was defined as the jejunum. The jejunum was then divided into thirds (proximal, mid-, and distal jejunum). Samples for mRNA analysis were taken from the middle portion of the midjejunal segment and immediately frozen in liquid nitrogen. Additional samples for histology were taken from the same location and placed in phosphate-buffered Formalin. The remainder of the midjejunal segment was then flushed with cold saline (9 gl) and weighed. The mucosa was scraped, homogenized in phosphate buffer containing protease inhibitors (9), and frozen at −70°C until analyses were performed.

### Analyses

#### Histological analysis.

Histological analysis of the jejunal samples was processed and stained with hematoxylin and eosin as previously described (13, 30). For each animal, 100 villi were measured, and the crypt depth was determined at 500 locations.

#### Measurement of LPH enzyme activity. LPH enzyme activity (μmol glucose min⁻¹·g protein⁻¹) of mucosal homogenates was measured and converted to micromoles glucose per minute per gram mucosa as previously described (9, 12, 13). The latter value was then used to calculate the absolute synthesis rate (synthesis rate in 1 g of mucosa) of each LPH polypeptide (see below).

#### Measurement of steady-state mRNA abundance.

RNA was isolated by the guanidine isothiocyanate-cesium chloride method and fractionated and blotted as previously described (13, 29). Radioactive probes for LPH mRNA and elongation...
In previous studies with anesthetized animals, we were able to obtain multiple tissue samples during an infusion and could therefore subject the kinetic data to compartmental analysis (8, 9). The intent of the present study was to measure fractional synthesis rates (FSR) of ally or enterally; thus, only a terminal tissue sample could be obtained. Therefore, the fractional synthesis rates (FSR) of both total mucosal protein and BB LPH synthesis were calculated using the isotopic enrichment of proLPHh as the denominator in the simplified equation

$$\text{FSR (%/day)} = \frac{S_0}{S_t} \times \frac{24/t}{100}$$

in which FSR is the fractional synthesis rate of total mucosal protein or BB LPH synthesized, $S_0$ is the tracer-to-tracee ratio of [3H]leucine in total mucosal protein or BB LPH after 6 h of infusion, $S_t$ is the tracer-to-tracee ratio of [3H]leucine in proLPHh, (the first detectable LPH precursor polypeptide synthesized) after 6 h of infusion, and t is labeling time, expressed in hours. We have previously used this same method to estimate FSR in conscious, unrestrained 2-wk-old pigs (10, 13).

The use of the equation involves two assumptions. First, as we have shown in rats and pigs (8–10), isotopic equilibration is achieved rapidly in both the mucosal free amino acid pool and proLPHh. Second, once isotopic equilibration is achieved in proLPHh, label incorporation into the BB protein is linear. Both assumptions have been shown to be valid (8–10). However, we have also shown a delay of ~1 h as label moves from proLPHh to proLPHc, and finally to the mature BB protein. Thus, for both treatment groups, estimating the FSR of BB LPH from 0 h results in a slight underestimate of the true rate of label incorporation into the BB protein and hence the true FSR.
RESULTS

There were no differences in body weight between the two treatment groups, either at the beginning of the study or at its termination (mean initial weight and final weight for parenterally fed animals were 1.7 ± 0.2 kg and 2.4 ± 0.2 kg, respectively; initial and final weights for enterally fed animals were 1.7 ± 0.2 and 2.5 ± 0.2 kg, respectively). Histologically, the villi were significantly (P < 0.05) shorter in parenterally fed animals (240 ± 31 µm) than in those fed enterally (356 ± 16 µm). No differences in crypt depth were observed (128 ± 4 and 135 ± 8 µm for parenterally fed and enterally fed pigs, respectively). However, the jejunal enterocytes appeared to be morphologically normal in both dietary treatment groups. The cells were columnar, with nuclei located close to the basolateral membrane.

The weight of the midjejunum was significantly (P < 0.05) lower in parenterally than in enterally fed animals (8 ± 1.5 and 17 ± 1.6, respectively). However, neither the weight of the scraped mucosa as a percentage of the weight of the intestinal sample nor the protein content of the mucosa differed. In parenterally fed animals, the weight of the mucosa was 5.5 ± 0.9 g, or 69 ± 1% of the weight of the jejunal segment. In enterally fed animals, the weight of the mucosa was 13.5 ± 1.7 g, or 77 ± 4% of the weight of the jejunal segment. The protein concentration of the mucosa of the parenterally fed animals was 90 ± 5 mg protein/g mucosa; that of the enterally fed group was 95 ± 5 mg protein/g mucosa. LPH enzyme activity (µmol·min⁻¹·g protein⁻¹) was, however, significantly higher (P < 0.05) in the parenterally fed group than in the enterally fed group, whereas total LPH activity (µmol·min⁻¹·jejunal segment⁻¹) was significantly lower (P < 0.05) in the parenterally fed group (Table 2).

The jejunal RNA concentration was 1.6 ± 0.40 and 1.4 ± 0.35 mg/g jejunum in parenterally fed and enterally fed animals, respectively. EF-1α mRNA levels did not differ between groups (data not shown). As shown in Table 2, LPH mRNA abundance relative to that of EF-1α also did not differ.

After sodium dodecyl sulfate-polyacrylamide gel electrophoresis, LPH polypeptides immunosolated from the solubilized, scraped mucosa separated into four bands, which we have previously identified as two precursor forms of BB LPH (proLPHh, 200 kDa; proLPHc, 220 kDa) and two forms of BB LPH: the 160-kDa polypeptide and a dimer of BB LPH with an apparent molecular mass of -240 kDa (Fig. 1) (8, 10, 13). In order of synthesis, the LPH polypeptides are proLPHh (the first detectable translation product), proLPHc (the complex glycosylated precursor), and, finally, the mature BB enzyme (8, 10, 13).

The relative abundance of proLPHh (i.e., the abundance of proLPHh relative to the total abundance of all four LPH polypeptides on a gel) was significantly (P < 0.05) higher in the parenterally fed than in the enterally fed animals (Table 2). The relative abundance of proLPHc and BB LPH was not significantly different between groups (Table 2).

The tracer-to-tracee ratios of the plasma free leucine pools of both treatment groups reached steady state within 1 h and did not differ at steady state (Table 3). However, the tracer-to-tracee ratio of the mucosal free leucine pools of the parenterally fed animals after 6 h of infusion was significantly higher (P < 0.05) than that of the enterally fed animals (Table 3). Thus the tracer-to-tracee ratio of the mucosal free leucine pool was 69 ± 7% of the plasma ratio in parenterally fed animals and 30 ± 7% of the plasma ratio in the enterally fed animals.

The tracer-to-tracee ratios of mucosal protein-bound leucine did not differ between treatment groups after 6 h of infusion (Table 3). However, the tracer-to-tracee ratio of protein-bound leucine expressed as a percentage of the corresponding mucosal free leucine pool was lower in parenterally fed animals (17 ± 0.8%) than in enterally fed animals (46 ± 5%). The tracer-to-tracee ratio of leucine in the earliest detectable precursor polypeptide (proLPHh) tended (P = 0.066) to be higher in parenterally fed than in enterally fed animals (Table 3). The tracer-to-tracee ratio of proLPHh-bound leucine expressed as a percentage of the tracer-to-tracee ratio of plasma free leucine was significantly (P < 0.05) higher in the parenterally fed than in enterally fed animals (72 ± 5% and 45 ± 6.5%, respectively). The

Table 3. Tracer-to-tracee ratio of leucine in plasma and mucosal free amino acid pools, mucosal protein and LPH polypeptides after 6-h infusion of [3H]leucine

<table>
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<tr>
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<th>Parenterally Fed</th>
<th>Enterally Fed</th>
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<tbody>
<tr>
<td>Plasma free leucine pool</td>
<td>4.4 ± 0.3</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>Mucosal free leucine pool</td>
<td>3.0 ± 0.2</td>
<td>1.5 ± 0.4*</td>
</tr>
<tr>
<td>Mucosal protein-bound leucine</td>
<td>0.52 ± 0.05</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>ProLPHh-bound leucine</td>
<td>3.1 ± 0.12</td>
<td>2.0 ± 0.4†</td>
</tr>
<tr>
<td>ProLPHc-bound leucine</td>
<td>1.9 ± 0.2</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>BB LPH-bound leucine</td>
<td>0.51 ± 0.07</td>
<td>0.49 ± 0.08</td>
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Data are means ± SE. *P < 0.05; †P = 0.066.
tracerto-tracee ratios of proLPH, bound leucine did not differ between groups (Table 3). The tracer-to-tracee ratio of proLPH, expressed as a percentage of the tracer-to-tracee ratio of proLPH, also did not differ between groups (61 ± 5% in parenterally fed animals and 73 ± 5% in enterally fed animals). As expected from previous studies (8, 10, 13), the tracer-to-tracee ratio of BB LPH-bound leucine did not reach steady state during the 6-h infusion (Table 3). As previously discussed, the tracer-to-tracee ratios in the 240-kDa dimer paralleled those of BB LPH (data not shown) (8, 10, 13).

The synthesis rates of total mucosal protein and BB LPH are shown in Fig. 2. The FSR of both total mucosal protein and BB LPH was significantly lower in parenterally fed (67 ± 7%/day, mucosal protein; 66 ± 1%/day, BB LPH) than in enterally fed animals (96 ± 7%/day, mucosal protein; 90 ± 1%/day, BB LPH).

The absolute synthesis rate (a measure of the amount of protein synthesized per gram of mucosal tissue) of total mucosal protein was significantly (P < 0.05) lower in parenterally fed (57 ± 4 AU) than in enterally fed animals (89 ± 8 AU). The total abundance of BB LPH in the midjejunum was significantly lower (P < 0.05) in parenterally fed than in enterally fed animals (97 ± 17 and 177 ± 31 AU, respectively). However, the absolute synthesis rate of BB LPH did not differ between the two treatment groups (on average, 12 ± 1.3 AU for both groups).

The total synthesis rate (a measure of the amount of protein synthesized in the midjejunal segment) of mucosal protein, as well as that of BB LPH, was significantly lower (P < 0.05) in parenterally fed piglets (317 ± 58 and 57 ± 6 AU for total mucosal protein and BB LPH, respectively) than in enterally fed piglets (1,190 ± 175 and 159 ± 25 AU for mucosal protein and BB LPH, respectively).

**DISCUSSION**

Parenteral nutrition has been associated with adverse effects on the small intestine in a wide variety of mammalian species (1, 3, 7, 14–16, 19, 20, 24–27). In adult laboratory animals without apparent intestinal disease, parenteral administration of an elemental diet seems to result in a pronounced reduction of intestinal mass, in decreased disaccharidase enzyme activities, and in altered intestinal morphology (3, 7, 14, 15, 24). In adult humans, the specific consequences of parenteral nutrition are extremely varied, perhaps because for most studies patients with intestinal diseases have been examined. In patients receiving parenteral nutrition for treatment of postoperative enterocutaneous fistulas, for example, intestinal morphological changes were observed (23). In contrast, in patients with inflammatory bowel disease, parenteral nutrition did not affect intestinal morphology but decreased BB hydrolase activities (17). Results from the only study that, to our knowledge, has examined the effect of parenteral nutrition in normal volunteers demonstrated intestinal morphological and functional changes paralleling those reported in laboratory animals (1). Unfortunately, BB disaccharidase activities were not determined.

The effect of parenteral nutrition on intestinal development and function in young mammals has received less attention than its effect on adults. Several studies have examined the effect of elemental regimes (i.e., glucose alone vs. glucose plus fat) in very young laboratory animals (26, 27), but none have examined the effect of parenteral vs. enteral alimentation. To our knowledge, the only study in children compares the effect of parenteral nutrition in individuals with short bowel syndrome or inflammatory bowel disease with individuals complaining of abdominal pain and/or chronic diarrhea who were given a complex oral diet (25). Thus, it is not clear whether the effects of parenteral nutrition in the young parallel the effects in adults. Furthermore, the mechanisms underlying these effects have not been examined.

The present study in neonatal pigs was undertaken to examine the effect of an elemental diet administered parenterally or enterally on small intestinal mucosal protein synthesis in general and on the steps of synthesis of a specific intestinal protein (BB LPH) that is of vital importance to young animals. Piglets were chosen for the study because they are our best laboratory model for human intestinal development and function (2, 28). Furthermore, during infancy in piglets there is a rapid rate of somatic and splanchnic growth. This early rapid growth allows for the evaluation of the nutritional effects on the gastrointestinal tract over a short period of time. Of equal importance, by undertaking the study in apparently healthy neonatal animals, the effects of an elemental diet could be examined without the confounding effects of small intestinal disease or surgical resection.

Under the conditions of the present study, and as reported by other investigators, the route of nutrient administration had no effect on piglet growth as determined by whole body weight gain (20). However, the weight of the jejunum was significantly lower in parenterally fed than in enterally fed animals (20). Villus length was likewise significantly lower in parenterally fed than in enterally fed piglets, but crypt depth was...
unaffected by the route of nutrient administration (1, 15, 23, 24).

Neither the protein nor the RNA concentration differed significantly between treatment groups. As reported in rats, LPH enzyme activity (expressed as µmol·min⁻¹·g protein⁻¹) was significantly higher in parenterally fed than in enterally fed animals (5). However, because of the lesser total mucosal mass in the parenterally fed animals, LPH total activity was significantly lower in parenterally fed than in enterally fed piglets.

The most striking and important finding in the present study was that the absolute synthesis rate (synthesis rate per gram of mucosa) of total mucosal protein and that of BB LPH appeared to be individually and differently affected by the route of nutrient administration. The FSRs for total mucosal protein and BB LPH were on average 40% lower in parenterally fed than in enterally fed animals. The absolute synthesis rate of total mucosal protein was significantly lower in parenterally fed than in enterally fed animals. In contrast, the absolute synthesis rate of BB LPH did not differ between treatment groups. Because of the reduced size of the small intestine in the parenterally fed animals, the total synthesis rates (synthesis rate/midjejunal segment) of both total mucosal protein and BB LPH were lower than in enterally fed animals. These observations imply that LPH synthesis and presumably lactase digestion are less susceptible to the route of nutrient administration than overall intestinal mass and protein synthesis. Furthermore, the data suggest that although the small intestine cannot compensate for the intestinal “atrophy” resulting from parenteral nutrition, it partially compensates for the resulting reduced total abundance of at least one physiologically vital enzyme, BB LPH, by maintaining its absolute synthesis rate.

Similar examples of compensatory mechanisms in the small intestine have been reported in the hibernating ground squirrel. In these animals, pronounced small intestinal atrophy and a significant decrease in total BB absorption of 3-O-methylglucose occur during hibernation (4). However, 3-O-methylglucose absorption per gram is significantly higher in hibernating than in active animals. Thus, although the synthesis rate of this transport protein has not been determined and the mechanism is undefined, it appears that in the hibernating ground squirrel the villus enterocyte compensates for the loss of total nutrient absorption resulting from a decrease in intestinal mass by upregulating the rate at which nutrients are absorbed in a unit of tissue. Note, however, that the findings in the present study are not strictly parallel to intestinal changes occurring in the hibernating ground squirrel, for we did not measure lactose absorption but rather LPH synthesis rates.

Although from this study we cannot precisely define the mechanisms underlying the changes in protein synthesis rates observed in parenterally fed animals, it is interesting to note that the route of nutrient administration appears to preferentially affect posttranscrip-